SIIM CAIMI26 Conference on Artificial Intelligence in Medical Imaging
OCT 26-27 | University of Pennsylvania, Philadelphia, PA

Distinct Interpretable Prostate-Specific Membrane Antigen Positron Emission Tomography Phenotypes Predict Depth of Response and Durability After Lutetium-177 Radioligand Therapy

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Introduction/Background

Outcomes after ^{177}Lu-PSMA radioligand therapy (RLT) for mCRPC vary widely. Quantitative PSMA PET features have been associated with response, particularly higher baseline tumor uptake; however, the relative value of different interpretable PET metrics for predicting distinct treatment outcomes remains incompletely defined, and broad radiomic panels may overfit in small cohorts. We tested whether burden and uptake-heterogeneity features add discrimination beyond routine clinical variables (age, baseline PSA) for early biochemical response and treatment durability.

Methods/Intervention

Retrospective single-institution cohort of 51 mCRPC patients. Baseline PSMA PET/CT lesions were manually segmented (MIM; SUV threshold 3.0, minimum volume 0.5 cm³) with manual review and correction before RTSTRUCT export; automated downstream processing derived lesion count, bone lesion count/fraction, total tumor volume, uptake heterogeneity (Gini of per-lesion SUVmean×volume), and compartment entropy. Outcomes were PSA50 response (≥50% PSA decline at a 12-week landmark) and durability (time to next therapy, hospice, or death). For each pre-specified feature we measured the gain in discrimination when added to a clinical base (age, baseline PSA), using AUC (response) and Harrell C-index (durability; 0.5 = chance). Nested bootstrap cross-validation (200 resamples) gave 95% CIs and the fraction of resamples showing improvement.

Results/Outcome

Forty-six patients were durability-evaluable (21 events); 43 response-evaluable (26 responders). Clinical variables alone discriminated near chance (PSA50 response AUC 0.54; durability C-index 0.58). Adding uptake Gini raised PSA50 response discrimination to AUC 0.76 (ΔAUC +0.22; improved in 96% of resamples) but not durability. Conversely, adding lesion burden raised durability discrimination to C-index 0.72 (bone lesion count ΔC +0.14, 84%; total lesion count 0.70, +0.12, 80%) but not PSA50 response. Bone lesion fraction, compartment entropy, and total tumor volume improved neither. Confidence intervals were wide (Gini ΔAUC 95% CI −0.02 to +0.56), reflecting the small sample.

Conclusion

These exploratory findings suggest distinct interpretable PSMA PET phenotypes carry complementary, outcome-specific information: uptake heterogeneity for depth of early PSA response and lesion burden for durability, each beyond clinical variables. Given the wide confidence intervals, results are hypothesis-generating.

Statement of Impact

Matching interpretable imaging features to outcomes, rather than fitting broad radiomic panels, may yield more robust post-RLT risk models; prospective validation is warranted.

Keywords

PSMA PET; radioligand therapy; prostate cancer; radiomics; uptake heterogeneity; incremental discrimination